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EXAMINER

EWOLDT, GERALD R

ART UNIT PAPER NUMBER

1644

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/802,397

Applicant(s)

MOSER ET AL.

Examiner

G. R. Ewoldt, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 June 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,5,7,9,11,13,15,17,21,23,29,38,51 and 52 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1,5,7,9,11,13,15,17,21,23,29,38,51 and 52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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#### DETAILED ACTION

1. Claims 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 29, 38, 51 and 52 are pending and are being acted upon.
2. Applicant's amendment and remarks, filed 6/13/05, are acknowledged. In view of the instant amendment the previous rejections under the first paragraph (new matter) and the second paragraph of 35 U.S.C. 112 have been withdrawn.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 29, 38, 51 and 52, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that a DC hybrid comprising a proliferating DC would be capable of producing an anti-tumor response.

As set forth previously, A review of the specification discloses that only hybrid clone 38 of Example 12 was tested for the ability to produce any relevant anti-tumor activity. The clone comprised a fusion employing a DC generated after 10 days in culture with GM-CSF and TNF $\alpha$ . The DCs after culture were MHC Class II+, B7.1+, and B7.2+. There is no disclosure as to whether or not the DCs after 10 days in culture were proliferating or not. Given this combined disclosure, it is more likely than not that the DCs employed in the example were unstable mature DCs, particularly given the expression of costimulatory molecules B7.1 and B7.2 that are more likely to be found on mature, non-proliferating DCs (see, for example, Morelli et al. (2001) which teaches that only mature DCs express B7.2 (CD86), and Shortman et al. (2002) which teaches that mature DCs are non-proliferating). Most certainly it has not been established that the DCs employed in the experiment were the proliferating DCs of the claims.

As set forth in the second declaration of Inventor Moser, and the remarks of 2/07/05, the proliferating, less differentiated DCs of the claims are immature DCs. There is no evidence of record, however, that an immature DC (and, thus, a DC/tumor hybrid comprising an immature DC) would be capable of producing the required response. The prior art appears to teach the opposite. See, for example, Jonuleit et al. (2000) which teaches that stimulation of naive T cells with immature DCs results in T cells that are irreversibly proliferation impaired and produce IL-10 (see Results).

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Dhodapkar et al. extend these findings by showing that immature DCs *in vivo* lead to antigen-specific T cell inhibition (see Results, particularly Figure 2B). Again, the reference teaches that immature DCs would not likely produce an anti-tumor response. Even the Inventors' own work confirms the finding that immature DCs are not inducers of an immune response, see de Heusch et al. 2004 (Figure 3F).

It is the Examiner's position then that the limited disclosure of the instant specification provides insufficient support for the method of the instant claims. Thus, in view of the quantity of experimentation necessary, the lack of any working examples, the unpredictability of physiological activity, and the contrary teachings of the prior art, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 5/13/05, have been fully considered but they are not persuasive. Applicant argues that the instant amendment overcomes the rejection, specifically, the amending of the use of proliferating DCs to DCs.

A review of the specification discloses the DCs are defined DCs or any DC progenitor. Accordingly, the rejection has been maintained because the claims still encompass the use of proliferating DCs in the claimed method.

5. The following are new grounds for rejection necessitated by Applicant's amendment.

6. Claims 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 29, 38, 51 and 52, are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method comprising preparing DCs by differentiating *in vitro* proliferating DC precursors isolated from bone marrow, lymph, or blood (Claim 1).

B) A method wherein DCs are prepared by culturing proliferating DC precursors isolated from bone marrow, lymph, or blood in the presence of cytokines so as to induce differentiation (Claim 38).

Applicant indicates that support for the limitations can be found at page 66 of the specification.

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A review of page 66 reveals only a vague teaching that previous experiments suggest that fusion partners should be proliferating cells of DCs at a more immature stage.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 21, 23, 29, 51, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992) and U.S. Patent No. 5,976,546.

Guo et al. teaches a plurality of hybrids (or hybridomas) comprising a bone marrow derived antigen-presenting B cell and an immortal tumor cell (see particularly page 520, columns 2-3, 11.). The reference teaches that the hybrids comprise cells that express both tumor-specific antigens and the machinery for antigen presentation (see particularly page 518, column 1), that said hybrids are immunogenic, and that said hybrids induce a protective anti-tumor immune response that might otherwise "escape immune surveillance because they do not express signals that are essential for activation of the host immune system" (see particularly page 520, column 1, and page 518, column 1) upon administration to a subject. Finally, the reference teaches that the fused hybrids "may have broad clinical applications and may provide a useful strategy for cancer immunotherapy" (page 520, column 1).

The reference teaching differs from the claimed invention only in that it does not teach the use of a DC as the antigen presenting component of the hybrid nor the isolation of the DC from blood.

Sornasse et al. teaches that, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo* (see particularly pages 16-17, Results). The reference teaches the superiority of DCs over B cells for *in vivo* use, "Our data emphasize the main role of DC in initiating primary responses in

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vivo" (see page 18, column 1).

The '546 patent teaches that blood is a convenient source of DCs (see particularly, column 5, lines 20-28). Also note that it is clear that the reference anticipates the use of human DCs (obtained from human blood) given the teachings of prostate cancer and HIV (human diseases) and HLA (human) antigens.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a plurality of hybrids (or hybridomas) comprising a bone marrow derived antigen-presenting B cell and an immortal tumor, said hybrids comprising cells that express both tumor-specific antigens and the machinery for antigen presentation, as taught by Guo et al., substituting a human DC (obtained from human blood for convenience, as taught by the '546 patent) for the B cell in said hybrid, as taught by Sornasse et al., and administer said product to a subject for production of an anti-tumor response. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution because, while both B cells and DCs are capable of inducing IL2 secretion *in vitro*, DCs induce a more vigorous response, including a Th1 response, *in vivo*, as taught by Sornasse et al. "Our data emphasize the main role of DC in initiating primary responses *in vivo*". Note that the blood of the '546 patent would comprise an isolated DC as well as the only two known subtypes of DC, i.e., myeloid and lymphoid, both of which derive from bone marrow.

9. Claims 5, 7, 9, and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992) and U.S. Patent No. 5,976,546, as applied to Claims 1, 21, 23, 29, 51, and 52 above, and in further view of U.S. Patent No. 5,851,756.

Guo et al., Sornasse et al., and the '546 patent have been discussed, above. The references differ from the claimed invention in that they do not teach the induction of DC characteristics before using said hybrids or hybridoma, nor the induction of said characteristics using GM-CSF.

The '756 patent teaches the induction of DC characteristics using GM-CSF (see particularly Example I). The reference further teaches that DC exist in relatively small numbers in blood, thus the induction of DC (and thus, DC characteristics)

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in GM-CSF before use provides a method to increase the number of said DCs (see particularly column 4, line 63 - column 5, line 9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a plurality of hybrids (or hybridomas) comprising a bone marrow derived antigen-presenting B cell and an immortal tumor cell, said hybrids comprising cells that express both tumor-specific antigens and the machinery for antigen presentation, as taught by Guo et al., substituting a human DC induced with GM-CSF before use, as taught by the '756 patent, for the B cell in said hybrid, as taught by Sornasse et al. and the '546 patent, and administer said product to a subject for production of an anti-tumor response. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution as set forth in section 8 above. One of ordinary skill in the art at the time of the invention would have been motivated to induce DC (and thus, DC characteristics) with GM-CSF before use because DC exist in relatively small numbers in blood, thus, the induction of DC in GM-CSF before use provides a method to increase the number of said DCs, as taught by the '756 patent.

10. Claims 11, 13, 15, 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo et al. (1994, IDS) in view of Sornasse et al. (1992) and U.S. Patent No. 5,976,546, as applied to Claims 1, 21, 23, 29, 51, and 52 above, and in further view of U.S. Patent No. 5,637,483.

Guo et al., Sornasse et al., and the '546 patent have been discussed, above. The references differ from the claimed invention in that they do not teach the treatment of the hybrids or hybridomas with irradiation before using to prevent proliferation, nor do they teach administration by parenteral injection.

The '483 patent teaches the treatment of a tumor cell-containing anti-tumor vaccine with irradiation before using to prevent proliferation, and administration of said cell vaccine by parenteral injection (see particularly column 3, lines 65-67 and column 14, lines 3-4).

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a plurality of hybrids (or hybridomas) comprising a bone marrow derived antigen-presenting B cell and an immortal tumor cell, said hybrids comprising cells that express both tumor-specific antigens and the machinery for antigen presentation, as taught by Guo et al., substituting a human DC obtained from blood for the B cell in said hybrid, as taught by Sornasse et al. and the '546 patent, treating the hybrids (or hybridomas) with irradiation before using, and administration of said cell vaccine by parenteral injection, as taught by the '483 patent, and administering said product to a subject for production of an anti-tumor response. One of ordinary skill in the art at the time of the invention would have been motivated to make said substitution as set forth in section 8 above. One of ordinary skill in the art at the time of the invention would have been motivated to treat the hybrids (or hybridomas) with irradiation before using to prevent proliferation, as taught by the '483 patent. One of ordinary skill in the art at the time of the invention would have been motivated to administer said hybrids (or hybridomas) by parenteral injection because this is the most well-known form of cell-based therapeutic administration.

11. No claim is allowed.

12. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


13. No claim is allowed.



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14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

15. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.

  
8/12/08

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